CLINICAL RESEARCH STUDY

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Risk of Recurrent Venous Thromboembolism: A Danish Nationwide Cohort Study

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ABSTRACT

PURPOSE: In this study, we aimed to estimate recurrence risk after incident venous thromboembolism, stratified according to unprovoked, provoked, and cancer-related venous thromboembolism in a prospective cohort of inpatients and outpatients receiving routine care.

METHODS: We linked nationwide Danish health registries to identify all patients with incident venous thromboembolism from January 2000 through December 2015. Rates of recurrence were calculated and Cox regression was used to compute hazard ratios (HRs) with 95% confidence intervals (CIs) by incident venous thromboembolism type after adjusting for coexisting risk factors.

RESULTS: The study included 73,993 patients with incident venous thromboembolism (54.1% females; mean age, 62.3 years). At 6-month follow-up, rates per 100 person-years were 6.80, 6.92, and 9.06 for provoked, unprovoked, and cancer-related venous thromboembolism, respectively. At 10-year follow-up, corresponding rates were 2.22, 2.84, and 3.70, respectively. Additionally, at 6-month follow-up, hazard rates of recurrence were comparable for patients with unprovoked venous thromboembolism 1.01 (95% CI, 0.92-1.11) and provoked. At 10-year follow-up, unprovoked venous thromboembolism (HR, 1.17; 95% CI, 1.12-1.23) and cancer-related venous thromboembolism (HR, 1.21; 95% CI, 1.12-1.32) were associated with higher risk of recurrence compared with that found in provoked venous thromboembolism.

CONCLUSIONS: In this nationwide cohort, patients with cancer-related venous thromboembolism had the highest risk of recurrence. At 6-month follow-up, there were similar risks of recurrence for patients with unprovoked and provoked venous thromboembolism. At 10-year follow-up, recurrence risks were similar for patients with unprovoked venous thromboembolism and patients with cancer-related venous thromboembolism. High recurrence risks in all categories indicate that further research is needed to optimize duration of extended anticoagulation for these patients.

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INTRODUCTION

Venous thromboembolism, comprising deep vein thrombosis and pulmonary embolism, is the third leading vascular disease after myocardial infarction and stroke, with rates of 1-3 per 1000 person-years.[1] Patients with venous thromboembolism carry a substantial risk of recurrence, with a cumulative incidence up to nearly 40% after 10 years with associated high mortality.[2] However, recurrent venous thromboembolism is largely preventable if patients receive extended-duration anticoagulation therapy. Continued anticoagulation after an incident venous thromboembolism reduces the risk of recurrence,[3] but the protective effect must be carefully weighed against the risk of anticoagulant-related bleeding.

CLINICAL SIGNIFICANCE

- The risk of recurrence after incident venous thromboembolism is high.
- Recurrence risk is highest for patients with cancer-related venous thromboembolism, closely followed by patients with unprovoked venous thromboembolism.
- We may need to rethink arbitrary categorization of patients with incident venous thromboembolism.
- Optimization of duration of extended anticoagulation for patients with venous thromboembolism is needed.

Patients with venous thromboembolism are heterogeneous, and recurrence risk varies considerably according to patient characteristics.[4–6] Ideally, risk stratification would identify patients with a high risk of recurrence requiring continued treatment and, conversely, patients with a shorter, time-limited need for treatment. In this study, we estimate the risk of recurrence after incident venous thromboembolism, stratified according to unprovoked, provoked, and cancer-related venous thromboembolism, using contemporary data from a nationwide Danish cohort.

MATERIAL AND METHODS

This study was an observational cohort study analyzing Danish nationwide administrative registry data to estimate risk of venous thromboembolism recurrence based on hospital diagnoses.

Setting and Data Sources

We used data from 3 Danish nationwide registries: (1) the Danish Civil Registration System,[7] which provides information on sex, date of birth, vital status, and emigration status; (2) the National Patient Register[8] (established in 1977), which includes dates of admission and discharge diagnoses classified according to the International Classification of Diseases (ICD) for more than 99% of hospital admissions in Denmark; and (3) the Danish National Prescription Registry,[9] which holds information on purchase date, Anatomical Therapeutic Chemical (ATC) classification codes, and package size for every prescription claimed since 1994. All codes used in this study are presented in Supplementary Table 1 (available online).

Study Population

We identified eligible venous thromboembolism patients from the National Patient Register. We included all patients with incident venous thromboembolism from January 2000 through December 2015, excluding emergency department diagnoses due to their low positive predictive value of 31%.[10] To ensure possible coding of risk factors in the national registries before the incident venous thromboembolism, we excluded patients who had lived in Denmark for less than 1 year before the incident venous thromboembolism. Because of their continued indication for anticoagulation, we also excluded patients with a diagnosis of atrial fibrillation before incident venous thromboembolism and patients on oral anticoagulant (OAC) treatment within the past year before incident venous thromboembolism. Finally, we excluded portal vein, retinal vein, and cerebral vein thrombosis because such events represent distinct diseases.[11]

Classification of Incident Venous Thromboembolism

In accordance with contemporary guidelines,[12,13] we classified venous thromboembolisms as 'cancer-related' (excluding nonmelanoma skin cancer), 'provoked,' or 'unprovoked.' Venous thromboembolisms occurring in patients with cancer were classified as cancer-related, regardless of other risk factors. Venous thromboembolisms occurring in patients without cancer or any provoking factor were classified as unprovoked. In patients without cancer, a venous thromboembolism occurring in the presence of 1 or more provoking factors was defined as provoked (Table 1 presents a list of provoking factors).

Because there is no universally accepted definition of "provoked" venous thromboembolism, classification of risk factors as either 'temporary' or 'persistent' was made based on recommendations from the International Society on Thrombosis and Haemostasis,[14] in combination with relevant guidelines and previous literature [6,13–16] (Supplementary Figure, available online). Temporary risk factors were defined as recorded within 3 months before the index event.[14] Cancer diagnoses were restricted to diagnoses given within 1 year before the index event to ensure that the diagnosis reflected active cancer. All other persistent risk factors were defined as registered at any given time before the index event.[14] The Danish National Prescription Registry was used to determine medical treatment status based on prescription claims within 1 year before incident venous thromboembolism.